REMARKS

This paper is being filed in response to the Office Action dated December 31, 2002 that was issued in the above-identified application. Applicants request a three-month extension of time and enclose the fee required under 37 C.F.R. §1.17(a)(3). Applicants respectfully request reconsideration of the above-identified application in light of the amendments and remarks presented in the instant Amendment.

Claims 138-147 are pending in the instant application. Claims 138-147 have been amended. The amended claims are supported by the specification as originally filed, *inter alia*, at page 15, lines 8-22 and, therefore, do not constitute new matter. Claims 148-151 have been added. The new claims are supported by the specification as originally filed, and, therefore, do not constitute new matter. Claims 138-151 will be pending upon entry of the instant amendments.

Rewritten specification paragraphs and claims appear respectively in the preceding "IN THE SPECIFICATION" and "IN THE CLAIMS" sections. Attached hereto is a marked-up version of the changes made by the instant amendment captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE" and is included pursuant to 37 C.F.R. §1.121(c)(ii). Should any discrepancies be discovered, the version presented in the preceding "IN THE SPECIFICATION" and "IN THE CLAIMS" sections shall take precedence.

The amendments to the specification made herein correct certain typographical and clerical errors and are fully supported by the specification as filed. Support for the amendments to Examples VIII, IX, X, XI, and XII are supported by, *inter alia*, the original Examples VIII, IX, X, XI, and XII respectively. For example, as originally filed, the description states that "[t]he formulations of Examples VIII, IX, and X include bismuth sulfate." Page 53,

line 2. In addition, Examples XI and XII recite the addition of bismuth sulfate at page 56, lines 10-11 and page 57, lines 10-11 respectively. Support for the amendments to Examples XIII and XIV are supported by, *inter alia*, the original Examples XIII and XIV respectively. For example, one of ordinary skill in the art would recognize that the addition of bismuth citrate and citric acid would result in the formation of bismuth citrate as chelate in solution. Therefore, the specification amendments made herein do not constitute new matter.

Support for new claim 148 can be found in the specification, *inter alia*, at page 23, line 14 to page 24, line 13 and Example I. Support for new claim 149 can be found in the specification, *inter alia*, at page 23, line 14 to page 24, line 13 and Example III. Support for new claim 150 can be found in the specification, *inter alia*, at page 23, line 14 to page 24, line 13 and Example I. Support for new claim 151 can be found in the specification, *inter alia*, at page 20, line 12 to page 21, line 6 and Example VIII.

As a preliminary matter, Applicant wishes to thank the Examiner for responding to Applicant's inquiry regarding the status of claims 88-96 and 129-137. The Examiner has now grouped claims 88-96 in Groups I-IV and V and grouped claims 129-137 in Group IX. Although Applicant has not presently elected these claims, the Examiner's remarks will assist Applicant in determining which claims to prosecute together in one or more divisional applications. Applicant also wishes to thank the Examiner for acknowledging Applicant's priority claims.

An objection has been raised against claims 143-147 under 37 C.F.R. § 1.75(c) for allegedly being of improper dependent form by failing to further limit the subject matter of earlier claims. The Examiner has alleged that claims 143-147 further limit the use of the subject matter of claim 138, but do not further limit the composition of the claimed aqueous solution.

Applicant traverses this objection and assert that claims 143-147, as amended herein, fully comply with 37 C.F.R. § 1.75(c). Therefore, Applicant respectfully requests withdrawal of this objection.

Claims 139 and 142 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Examiner has alleged that the phrase "the dosage form or the oral liquid dosage form" in these claims lacks proper antecedent basis.

Applicant traverses this objection and assert that claims 139 and 142, as amended herein, are clear and definite and fully comply with 35 U.S.C. § 112, second paragraph. Amended claims 139 and 142 do not recite this phrase. Therefore, Applicant respectfully requests withdrawal of this rejection.

Claims 138-147 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Japanese Application No. 6215322 by Nakazawa Shinzo and Kuno Satoshi (abstract only; hereinafter "Satoshi"). The Examiner has alleged that Satoshi teaches an oral aqueous solution comprising bile acids such as UDCA and dextrins such as amylodextrin. The Examiner has also alleged that Satoshi teaches this bile solution can be formulated for internal use without pH adjustment.

Applicant traverses this rejection and asserts that claims 138-147 are patentable over Satoshi. For a reference to anticipate a claim, it must teach each and every limitation of the claim. Claims 139-147 are dependent on independent claim 138. Therefore, these remarks will address primarily claim 138.

Solutions of the instant claimed invention do not contain alcohol. However, the compositions of Satoshi all appear to contain alcohol, *e.g.* ethanol. Satoshi appears to teach water-based bile acid solution that may be prepared by either a fluidized layer granulation

method or a dispersion method. *See e.g.* Satoshi, abstract. In the fluidized layer granulation method, Satoshi teaches the addition of ethanol. *See e.g.* Satoshi, machine assisted translation, page 6, lines 28-31. Throughout the disclosure, the compositions of Satoshi are described as "liquor" composition. *See e.g.* Satoshi, machine-assisted translation, page 6, line 36 to page 7, line 5; page 8, lines 2-3; Tables 1 and 2; and claim 1. Applicant asserts that it is well known to those of ordinary skill in the art that once alcohol is added to an aqueous solution, an azeotropic mixture is formed. Therefore, Satoshi fails to teach any solution that lacks ethanol and, consequently, fails to teach each and every limitation of claim 138. Applicant, therefore, respectfully requests withdrawal of this rejection of claims 138-147.

New claims 148, 149, and 150 are each independent and are patentable over Satoshi. Satoshi teaches that the weight ratio of dextrin to bile acid must be 30 or more **and** that the concentration of dextrin must be less than or equal to 35%. *See e.g.* Satoshi, machine-assisted translation, page 5, lines 3-4 and claim 1. The combination of these two requirements would indicate to one skilled in the art that the maximum bile acid concentration possible according to Satoshi is 1.167%.

The instant invention is a novel improvement over the composition of Satoshi in several ways. First, the instant invention teaches clear aqueous solutions of bile acid wherein the weight ratio of the aqueous soluble starch conversion product to bile acid is less than 30, thus permitting the use of less aqueous soluble starch conversion product per gram of bile acid. This is taught, for example, at page 23, lines 14-18, where the ratio of maltodextrin to bile acid is preferably 25:1.

Second, according to the instant invention, the concentration of aqueous soluble starch conversion products can be at least as high as 50% (maltodextrin, *inter alia*, page 23, lines

14-18) to 80% (liquid glucose, *inter alia*, page 23, line 21 to page 24, line 3). This is advantageous because it allows more bile acid to be dissolved in solution.

Third, the instant invention teaches clear aqueous solutions of bile acids, wherein the concentration of bile acid is up to about 2 % (W/W). *See* page 23, lines 14-18. Therefore, the instant claims are novel over Satoshi since Satoshi fails to teach bile acid solutions wherein (i) the weight ratio of starch to bile acid is less than 30 (Claim 148), (ii) the concentration of dextrin is more than 35 % (Claim 149), or (iii) the bile acid concentration is more than about 1.17 % (Claim 150).

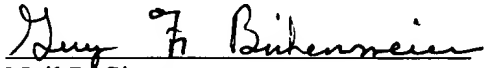
New independent claim 151 recites "an aqueous soluble derivative of a bile acid, a bile acid salt, a bile acid conjugated with an amine by an amide linkage, and combinations thereof." The instant invention discloses bile acid salts, *inter alia*, at page 20, line 12 to page 21, line 6 and Example VIII. Satoshi fails to teach aqueous soluble derivatives of bile acid, bile acid salts, or amine-conjugated bile acids. Therefore, Satoshi fails to anticipate claim 151.

In summary, claims 143-147 are in proper dependent form and claims 138-151 are clear and not anticipated by Satoshi since Satoshi fails to teach each and every limitation of the claimed invention. Therefore, Applicant believes that claims 138-151 are in condition for allowance and respectfully requests prompt favorable action.

Applicant has enclosed the fee required under 37 C.F.R. §1.17(a)(3). Applicant does not believe that any additional fees are required with this communication. Nevertheless, the Commissioner is hereby authorized to charge any fees due with this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Please credit any overpayment of fees associated with this filing to the above-identified deposit account. A duplicate of this page is enclosed.

Respectfully submitted,

June 30, 2003



Neil P. Sirota
PTO Reg. No. 38,306
Attorney for Applicant

Guy F. Birkenmeier
PTO Reg. No. 52,622
Agent for Applicant

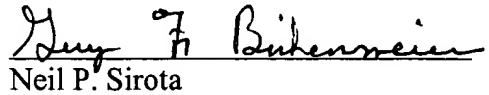
BAKER BOTTS, L.L.P.
30 Rockefeller Plaza
New York, NY 10112
(212) 408-2548

Enclosure

Applicant has enclosed the fee required under 37 C.F.R. §1.17(a)(3). Applicant does not believe that any additional fees are required with this communication. Nevertheless, the Commissioner is hereby authorized to charge any fees due with this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Please credit any overpayment of fees associated with this filing to the above-identified deposit account. A duplicate of this page is enclosed.

Respectfully submitted,

June 30, 2003



Neil P. Sirota
PTO Reg. No. 38,306
Attorney for Applicant

Guy F. Birkenmeier
PTO Reg. No. 52,622
Agent for Applicant

BAKER BOTTS, L.L.P.
30 Rockefeller Plaza
New York, NY 10112
(212) 408-2548

Enclosure

OIPE JC35 JUL 0 3 2003 PATENT & TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

This marked-up version was prepared with DeltaView software (v2.7). In this section, added text is marked with double underlining. *e.g.* added text, and deleted text is marked by a single strikethrough, *e.g.* ~~deleted text~~.

IN THE SPECIFICATION

The paragraph beginning at page 53, line 1 and ending at page 53, line 5 has been **amended** as follows:

Example VIII: Mixture Solution

The formulations of Examples VIII, IX, X, XI, and ~~X~~XII include aqueous soluble bismuth ~~sulfate~~chelate. In each of these examples, solution dosage forms were prepared by adding an amount of an ammonium salt of bismuth sulfate sufficient to provide the indicated amount of bismuth sulfate.

The paragraph beginning at page 53, line 6 and ending at page 53, line 14 has been **amended** as follows:

Solution dosage forms that were prepared according to the following guidelines did not show any

precipitation at any pH within the selected desired range of pH values.

UDCA	5 g
CDCA	5 g
Bismuth ~~citrate~~sulfate	5 g
Corn syrup solid	260 g
Citric acid	q.s.
Purified water to make	1.0 L

The paragraph beginning at page 53, line 15 and ending at page 53, line 19 has been **amended** as follows:

The UDCA and CDCA were first dissolved in 1.5 mL of a 1N NaOH solution. Next, to the resulting clear solution were added the bismuth ~~citrate~~sulfate and 150 mL of water. Then, the corn syrup solid was added portion by portion with vigorous agitation. The resulting solution was titrated to pH 4 with citric acid. Purified water was added to adjust the total volume to 1.0 L.

The paragraph beginning at page 54, line 1 and ending at page 54, line 10 has been **amended** as follows:

Example IX: UDCA-Syrup (20 g UDCA/L)

Solution dosage forms that were prepared according to the following guidelines did not show any precipitation at any pH within the selected desired range of pH values.

UDCA	20 g
1 N NaOH	60 mL
Maltodextrin	700 g
Bismuth ~~citrate~~sulfate	4 g
Citric acid or lactic acid	q.s.
Purified water to make	1.0 L

The paragraph beginning at page 55, line 1 and ending at page 55, line 10 has been **amended** as follows:

Example X: UDCA-Syrup (20 g UDCA/L)

Solution dosage forms that were prepared according to the following guidelines did not show any

precipitation at any pH within the selected desired range of pH values.

UDCA	20 g
1 N NaOH	60 mL
Corn syrup solid	1,050 g
Bismuth ~~citrate~~sulfate	4 g
Citric acid or lactic acid	q.s.
Purified water to make	1 L

The paragraph beginning at page 56, line 1 and ending at page 56, line 9 has been **amended** as follows:

Example XI: UDCA-Thick Syrup (30 g UDCA/L)

Solution dosage forms that were prepared according to the following guidelines did not show any precipitation at any pH within the selected desired range of pH values.

UDCA	30 g
1 N NaOH	90 mL

Bismuth sulfate	4 g
Maltodextrin	1,050 g
Citric acid or lactic acid	50 g
Purified water to make	1.0 L

The paragraph beginning at page 57, line 1 and ending at page 57, line 9 has been **amended** as follows:

Example XII: UDCA-Thick Syrup (30 g UDCA/L)

Solution dosage forms that were prepared according to the following guidelines did not show any precipitation at any pH within the selected desired range of pH values.

UDCA	30 g
1 N NaOH	90 mL
Bismuth sulfate	4 g
Corn syrup solid	1,500 g
Citric acid or lactic acid	50 g
Purified water to make	1.0 L

The paragraph beginning at page 58, line 1 and ending at page 58, line 5 has been **amended** as follows:

Example XIII: UDCA-Paste (45 g UDCA/L)

The formulations of Examples XIII, XIV, XV, XVI, XVII, and ~~XVI~~XVIII include bismuth citrate as chelate. In each of these examples, solution dosage forms were prepared by adding an amount of an ammonium salt of bismuth citrate sufficient to provide the indicated amount of bismuth citrate.

The paragraph beginning at page 60, line 1 and ending at page 60, line 9 has been **amended** as follows:

Example XIV: UDCA-Paste (45 g UDCA/L)

Solution dosage forms that were prepared according to the following guidelines did not show any precipitation at any pH within the selected desired range of pH values.

UDCA	45 g
1 N NaOH	135 mL
Bismuth citrate	10 g

Corn syrup solid	2,300 g
Citric acid or lactic acid	50 g
Purified water to make	1.0 L

IN THE CLAIMS

Claims 138-147 have been **amended** as follows:

138. [AMENDED] A clear aqueous solution comprising;

(i) a first material selected from the group consisting of a bile acid, an aqueous soluble derivative of a bile acid, a bile acid salt, a bile acid conjugated with an amine by an amide linkage, and combinations thereof;

(ii) a second material selected from the group consisting of an aqueous soluble starch conversion product and/or an aqueous soluble non-starch polysaccharide; and

(iii) water,

wherein the first and second materials both remain in solution for all pH values of the solution within a selected range of pH values and the solution is free of alcohol.

139. [AMENDED] The solution of Claim ~~138~~138, wherein the ~~dosage form~~solution is selected form the group consisting of a syrup, a thick syrup, and a paste.

140. [AMENDED] The solution of Claim ~~138~~138, wherein the first material is selected from the group consisting of ursodeoxycholic acid, chenodeoxycholic acid, cholic acid, hyodeoxycholic acid, deoxycholic acid, 7-oxolithocholic acid, lithocholic acid, iododeoxycholic acid, iocholic acid, tauroursodeoxycholic acid, taurochenodeoxycholic acid, taurodeoxcycholic acid, glycoursodeoxycholic acid, taurocholic acid, glycocholic acid, their derivatives at a hydroxyl or carboxylic acid group on the steroid nucleus, their salts, or their conjugates with amines.

141. [AMENDED] The solution of Claim ~~138~~138, wherein the second material is selected from the group consisting of maltodextrin, dextrin, corn syrup, corn syrup solid, soluble starch, and dextrans.

142. [AMENDED] The solution of Claim ~~138~~138, wherein the ~~oral liquid dosage form~~solution comprises one or more additional bile acids, aqueous soluble derivatives of bile acid, bile acid salts, and amine-conjugated bile acids conjugated by an amide linkage.

143. [AMENDED] The solution of Claim 138 ~~wherein the solution is capable of~~further comprising an agent having anti-inflammatory activity.

144. [AMENDED] The solution of Claim 138 ~~wherein the solution is capable of~~further comprising an agent having analgesic activity.

145. [AMENDED] The solution of Claim 138 ~~wherein the solution is capable of~~further comprising an agent having anticonvulsant activity.

146. [AMENDED] The solution of Claim 138 ~~wherein the solution is capable of~~further comprising an agent having prolonging survival time in hypoxic conditions.

147. [AMENDED] The solution of Claim 138~~—wherein the solution is~~ further comprising an agent capable of alleviating or ameliorating a condition selected from the group consisting of stomatitis, gingivoglossitis and toothache.